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## Original Articles

# Extracorporeal Membrane Oxygenation: Beneficial Strategy for Lung Transplant Recipients

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**Abstract:** The role of extracorporeal membrane oxygenation (ECMO) as a therapeutic strategy has been very well documented for over a decade now with consistently positive remarks. The aim of the present study was analyzing the outcome of ECMO application in our lung transplant program, especially the feasibility and safety of our ECMO approach. Therefore, we retrospectively analyzed the data of 15 patients recipients requiring ECMO support. We analyzed clinical data, complications, and survival of the lung-transplanted population that needed ECMO support at our institution from 2006–2009. During that period, 19 applications of ECMO were done on 15 adult patients with the following indications: primary graft dysfunction (10 patients), "bridge to transplantation" (five), pulmonary hypertension (three), and severe acute respiratory distress syndrome (one). At 28 days, the overall survival was 93% (14 of 15 patients) and 12 of these patients (80%) survived at least 6 months. Complications included acute renal insufficiency with temporary need of renal replacement therapy (53%), bleeding (33%), critical illness polyneuropathy (66%), and reversible thrombocytopenia (73%). Based on the evaluation of the patients in this analysis, ECMO seems to be a safe therapeutic approach in lung transplant recipients with severe respiratory failure directly after transplantation. **Keywords:** extracorporeal membrane oxygenation (ECMO), lung transplantation, outcome, primary graft dysfunction, pulmonary hypertension, acute respiratory distress syndrome (ARDS). *JECT. 2013;45:16–20*

The value of extracorporeal membrane oxygenation (ECMO) as a therapeutic modality for severe but potentially reversible respiratory failure has been shown recently with studies demonstrating survival rates as high as 70% (1–3). However, for lung transplant recipients, ECMO as a therapeutic strategy treating primary graft dysfunction (PGD) is scarcely studied (4–8).

After lung transplantation, PGD is an occasionally occurring, early complication with a reported incidence of 10–29% (9,10). Its pathophysiology as far it is understood today is multimodal encompassing donor and recipient properties as well as explantation and implantation course, summarized for example in Lee and Christie (11). The inflammatory reactions are much more complex and the damage is increased by graft-specific problems such as immunosuppression, the lack of lymphatic drainage, and the missing bronchial arterial circulation. Lung protective low tidal ventilation and extracorporeal gas exchange may be beneficial in early graft dysfunction and other inflammatory injury states and might improve short- and long-term outcomes (12–14). Still the potential benefits of ECMO and maximal lung protective ventilation are opposed by the major associated complications of severe bleeding and infection.

At our center, the lung transplantation program began on January 1, 1992. By December 31, 2009, 286 patients were transplanted. Between 2006 and 2009 we have performed 94 lung transplantations, 90 of which were bilateral (95.6%). A total of 15 recipients (15.9%) required ECMO support before or after transplantation. One patient underwent ECMO 10 years after lung transplantation, after blood aspiration during massive upper gastrointestinal bleeding.

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The aim of the present study was to analyze the outcome of ECMO application in our lung transplant program, especially the feasibility and safety of our ECMO approach. Therefore, we analyzed data of 19 consecutive ECMO applications in 15 patients in our lung transplant program between 2006 and 2009 at our intensive care unit.

## METHODS

After approval by the local ethics committee, which waived the need for written informed consent for this post hoc data analysis, patient data were analyzed from 19 consecutive ECMO applications in 15 adult patients in our lung transplant program from January 2006 to December 2009. Use of ECMO during lung transplantation surgery was not considered. Data were obtained from the local ECMO database and patient charts.

The following baseline data were collected and analyzed: age, gender, body mass index, underlying lung disease, transplantation type (unilateral or bilateral), Simplified Acute Physiologic Scale (SAPS) II score, and the pressure gradient of right ventricle/right atrium (RV/RA) by echocardiography.

The SAPS II is a scoring system of 17 variables, which predicts mortality in critically ill patients without having to specify a primary diagnosis and was developed and validated in 1993 with an area under the curve of .88 in the developmental sample and .86 in the validation sample (15).

The RV/RA pressure gradient indicates the gradient measured by echocardiography of RV pressure and RA pressure during systole and correlates well with pulmonary hypertension (16).

The collected data concerning the ECMO application were as follows: indication leading to ECMO (PGD, bridge to transplant, or pulmonary hypertension), duration of ECMO, duration of ventilation, major complications (such as bleeding, thrombocytopenia, and infection), and type of cannulation (venovenous [VV], venoarterial [VA], or venovenous–arterial [V-V-A]). Outcome measurements were need of renal replacement therapy, survival and mortality rates (intensive care unit [ICU] mortality, 28-day mortality, 3- and 6-month mortality, cumulative 6-month survival), and length of stay in the ICU.

VA, VV, and mixed V-V-A ECMO techniques were used depending on the underlying pathology. Three patients had conversion from V-V to V-V-A ECMO as a result of otherwise uncorrectable hypoxia.

A Bioline (heparin-bonded) Quadrox D Oxygenator (Maquet, Hirrlingen, Germany) and a Jostra Rotaflow centrifugal pump (Maquet) were used in all cases.

The tubing set and all connectors and cannulae were heparin-bonded from tip to tip. In most cases, a Biomedicus console (Medtronic, Minneapolis, MN) with an adapter for the Rotaflow Pump was used. By the end of 2009, we started using Rotaflow consoles as well. Heparin was administered in the absence of significant bleeding or after correction of coagulopathy and titrated to maintain an activated clotting time of 150–200 seconds.

There were additional strategies of the ECMO approach. V-A extension of the ECMO system was done if 88% $SaO_2$ could not be achieved with a V-V system. Negative or constant fluid balance during ECMO therapy was maintained. This is easier to target with a double-venous cannulation (permitting good venous return) and catecholamine support, both allowing for sufficient blood flow without fluid overload. The lack of lymphatic drainage of lung grafts reduces interstitial fluid clearance and will thus increase susceptibility to fluid overload. Anticipating this problem, we used in certain cases a priori a V-V-A ECMO to get better control of the blood flow through the lungs without compromising the systemic oxygen demand. The ECMO approach was accompanied by maximal lung protective ventilation (4–6 mL/kg body weight) with airway pressure release ventilation setting to avoid ventilator-induced lung injury and its consecutive tissue damage.

Weaning from ECMO support was considered when hemodynamic stability and improvement of lung function based on gas exchange, lung compliance, and pulmonary artery pressure occurred. During weaning from ECMO, the $FiO_2$ of the respirator was decreased to 60%. Then oxygenation by ECMO was stepwise decreased to 21% in the V-V system or to a postoxygenator $pO_2$ of 60–75 mmHg in the V-V-A system. Blood flow was also weaned to 1 L per minute and per inlet cannula (2 L in the case of V-V/V-A ECMO). As soon as termination criteria were fulfilled (i.e., sufficient gas exchange), anticoagulation was briefly stopped and ECMO cannulas were removed.

A brief, right–left shunt in the mixed V-V-A ECMO systems was used as an ultimate test for lung oxygenation before terminating ECMO.

Baseline, clinical, and ECMO data are shown as values presented in Tables 1–3. We analyzed overall and subgroup cumulative survival rates by Kaplan-Meier analysis.

## RESULTS

We performed 19 applications of ECMO on 15 adults who received 17 lung transplantations between January 2006 and December 2009. There were 15 bilateral and two single lung transplantations. Patients 10 and 11 needed bilateral and unilateral retransplantation, respectively, because of primary graft dysfunction (Table 1).

The patient's characteristics are shown in Table 1, outcome data in Table 2, and ECMO data in Table 3. Patients 2, 8, and 11 had two or three applications of ECMO.

**Table 1.** Baseline data.

| Patient No. | Age (years) | Gender (male/female) | Body Mass Index (kg/m$^2$) | Diagnosis | SAPS II (points) | Procedure | RV/RA (mmHg) |
|---|---|---|---|---|---|---|---|
| 1 | 64 | F | 25 | IPF | 62 | BL | 25 |
| 2 (I, II) | 41 | M | 28 | IPF | 50 | BL | 61 |
| 3 | 62 | F | 23 | IUP | 69 | RL | 63 |
| 4 | 32 | F | 20 | CF | 42 | BL | NK |
| 5 | 22 | M | 18 | CF | 11 | BL | 31 |
| 6 | 33 | M | 24 | CF | 57 | BL | NK |
| 7 | 58 | M | 31 | IUP | 24 | BL | 34 |
| 8 (I, II) | 62 | M | 28 | IPF | 24 | BL | 58 |
| 9 | 21 | F | 22 | CF | 31 | BL | 55 |
| 10 | 60 | M | 30 | IPF | 62 | 1. BL, 2. BL* | 32 |
| 11 (I, II, III) | 18 | F | 17 | CF | 35 | 1. BL, 2. RL* | 55 |
| 12 | 60 | F | 24 | sPH | 54 | BL | 60 |
| 13 | 17 | M | 23 | pPH | 8 | BL | 67 |
| 14 | 59 | M | 35 | sPH | 49 | BL | 84 |
| 15 | 63 | F | 27 | sPH | 54 | BL | 46 |

This table depicts the baseline characteristics of the 15 studied patients.
*Retransplantation.
SAPS, Simplified Acute Physiologic Scale; RV/RA, right ventricle/right atrium; F, female; M, male; IPF, idiopathic pulmonary fibrosis; IUP, usual interstitial pneumonia; CF, cystic fibrosis; sPH, secondary pulmonary hypertension; pPH, primary pulmonary hypertension; BL, bilateral lung transplantation; RL, right lung transplantation, I–III applications of extracorporeal membrane oxygenation; NK, not known.

The overall 28-day survival was 93% (14 of 15 patients) (see Figure 1). The overall ICU and the cumulative 3- and 6-month survivals were each 80%. The cumulative 6-month survival rates of the subgroups were as follows: severe pulmonary hypertension (100%, three of three patients), PGD (80%, four of five patients), and "bridge to transplantation" (80%, eight of 10 patients).

Among the ICU nonsurvivors, Patient 5 died from late graft dysfunction 2 months after transplantation, Patient 9 died from pulmonary infection with multiple organ failure, and Patient 10 died from uncontrollable hemorrhage after retransplantation.

Mean ECMO time was 7 ± 6 days for survivors vs. 18 ± 15 for nonsurvivors, and ICU stay was 44 ± 44 days for survivors vs. 29 ± 9 days for nonsurvivors.

The complications occurring during ECMO were infections (66%, 10 of 15 patients) and multiple organ dysfunctions (46.6%, seven of 15 patients). The micro-organisms responsible for infections were mostly undetectable, probably because all of the patients were treated with antibiotics. Therefore, there were only a small number of positive cultures: two cannula infections (coagulase-negative staphylococci), six positive hemocultures (four coagulase-negative staphylococci, one multiresistant *Pseudomonas aeruginosa*, and one *Escherichia coli* with extended-spectrum beta-lactamase) and four patients with pneumonia with multiresistant *P. aeruginosa*. Two of the three infections in the nonsurvivors were documented microbiologically.

Coagulase-negative staphylococci wound infections at the former cannulation site were observed in 20% of the patients.

**Table 2.** Outcome data.

| Q | Patient No. | 28-Day Survival | 3-Month Survival* | 6-Month Survival* | Cause of Death | ICU-LOS (days) | RRT (days) |
|---|---|---|---|---|---|---|---|
| q | 1 | Y | Y | Y | — | 19 | 0 |
| q | 2 (I, II) | Y | Y | Y | — | 59 | 0 |
| q | 3 | Y | Y | Y | — | 139 | 144 |
| q | 4 | Y | Y | Y | — | 20 | 0 |
| q | 5 | N | N | N | Graft dysfunction | 19 | 0 |
| q | 6 | Y | Y | Y | — | 19 | 9 |
| q | 7 | Y | Y | Y | — | 39 | 3 |
| q | 8 (I, II) | Y | Y | Y | — | 35 | 26 |
| q | 9 | Y | N | N | MOF | 32 | 32 |
| q | 10 | Y | N | N | Bleeding | 36 | 0 |
| q | 11 (I, II, III) | Y | Y | Y | — | 122 | 82 |
| q | 12 | Y | Y | Y | — | 47 | 24 |
| q | 13 | Y | Y | Y | — | 4 | 0 |
| q | 14 | Y | Y | Y | — | 7 | 3 |
| q | 15 | Y | Y | Y | — | 9 | 0 |

This table shows the outcome data.
*Post-extracorporeal membrane oxygenation (ECMO) survival. The Roman numerals I to III indicate the numbers of applications of ECMO.
ICU-LOS, intensive care unit length of stay; RRT, renal replacement therapy; Y, yes; N, no; MOF, multiple organ failure.

**Table 3.** Extracorporeal Membrane Oxygenation (ECMO) data.

| Patient No. | Indication | ECMO Type | ECMO (days) | Ventilation (days) | CIP | Infection | Bleeding | TC-penia |
|---|---|---|---|---|---|---|---|---|
| 1 | PGD | V-A | 4 | 20 | N | N | N | Y |
| 2 (I, II) | b/PGD | V-V ext./V-V-A | 12/5 | 59 | Y | Y | Y | Y |
| 3 | PGD | V-V-A | 14 | 139 | N | Y | N | N |
| 4 | b | V-V | 1 | 18 | N | Y | Y | Y |
| 5 | PGD | V-V | 1 | 19 | Y | Y | N | N |
| 6 | ARDS | V-V-A | 8 | 12 | Y | N | N | Y |
| 7 | b | V-V-A | 42 | 22 | Y | Y | N | Y |
| 8 (I, II) | b/PGD | V-V-A/V-V-A | 4/9 | 25 | Y | Y | Y | Y |
| 9 | PGD | V-V-A | 28 | 31 | Y | Y | N | Y |
| 10 | PGD | V-V-A | 25 | 32 | Y | Y | Y | Y |
| 11 (I, II, III) | PGD/b/PGD | V-V ext./V-V-A/V-V | 6/11/5 | 120 | Y | Y | N | Y |
| 12 | PH | V-V-A | 3 | 35 | Y | Y | N | Y |
| 13 | PGD | V-V | 2 | 2 | N | N | Y | N |
| 14 | PH | V-V ext. | 3 | 4 | N | N | N | Y |
| 15 | PH | V-V-A | 3 | 3 | Y | N | N | Y |

This table shows the ECMO-related data.
CIP, critically ill polyneuropathy; TC-penia, thrombocytopenia; PGD, primary graft dysfunction; b, bridging to TPL/re-TPL; PH, pulmonary hypertension; V-A ext., venoarterial extension; V-V ext., venovenous extension; V-V-A, venovenous arterial; Y, yes; N, no; TPL, transplantation.

Hemorrhage needing packed red cells and surgical revision was noted in 66% of the patients and was the same for survivors and nonsurvivors. Bleeding into the thoracic cavity occurred in five of 15 patients (33%), whereas one patient died a few hours after retransplantation from ECMO-induced, uncontrollable bleeding and coagulopathy. Four patients needed revision of the cannula insertion site. Transitory thrombocytopenia was observed in 12 of 15 patients (80%). None of the patients had heparin antibodies.

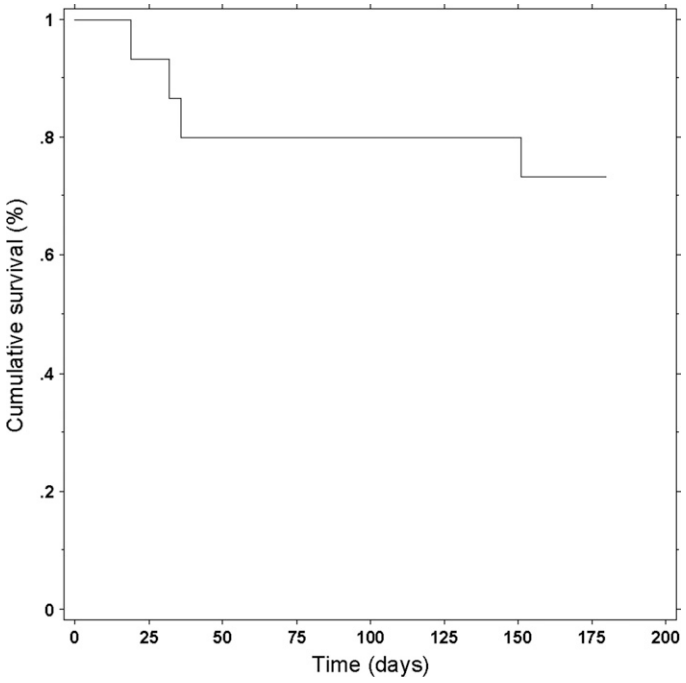


**Figure 1.** This figure displays the Kaplan-Meier cumulative survival curve of all patients. The overall cumulative 6-month survival rate was 80% (12 of 15 patients).

Acute kidney injury with consecutive renal replacement therapy was present in eight of 15 (53%) of the patients with a mean hemofiltration time of 37 ± 48 days. Three recipients needed hemodialysis after discharge from the ICU, and one patient needed hemodialysis after discharge from the hospital.

Critically illness polyneuropathy was present in 11 of 15 (73%) patients.

## DISCUSSION

The so far biggest sample size analyzed was published by Fischer and colleagues (5), where they used the data from the Extracorporeal Life Support Organization (ELSO) registry and found 151 lung transplant recipients with PGD treated with ECMO. Of these 42% survived to hospital discharge. Bermudez et al. (4) reviewed their single-center data from 1991–2006. In their collective 58 lung recipients needed an ECMO because of PGD out of a total of 763 lung transplantation. The 30-day survival of the patients who had ECMO was 56%. In our sample, the 28-day survival was 93% and the 6-month survival was 80%.

Comparing the complication rates of our study group with the ELSO registry population, the percentage of renal failure was higher (53% vs. 42%) and the bleeding rate was higher (66% vs. 52%) in our study.

In contrast to the published data, we prefer a cannulation mode that uses a combination of V-V and V-A ECMO. The reasoning behind that approach is as follows: the oxygenation of the transplanted lung is entirely dependent on pulmonary arteries and alveolar gas exchange because bronchial arteries are lacking. Moreover, inflammation increases oxygen consumption by lung tissue. Therefore, oxygen supply by pulmonary arteries to the graft is crucial, and V-V ECMO becomes problematic, because it is

by its nature at the brink of systemic hypoxia. On the other hand, V-A ECMO can safeguard systemic oxygen delivery, but the lungs are partially bypassed and therefore underperfused with oxygen depletion. Although "healing" is oxygen-dependent, the lungs might not recover under a V-A ECMO. In contrast, V-A ECMO is indicated in the case of severe posttransplant pulmonary hypertension to protect the new lung from hyperperfusion resulting in pulmonary edema aggravated through the absence of lymphatic drainage hampering the clearance of lung interstitium. Combining the two techniques, one has the possibility to regulate the amount of blood flow through the lungs and the systemic oxygenation. This approach was analyzed by Stöhr et al. in 2011 (17), in which they showed a trend also statistically not significant to better survival in patients with acute respiratory distress syndrome using a V-V-A ECMO approach.

The limitations of our study are its retrospective design and the small sample size.

In summary, our results show a reasonable survival of lung transplant recipients needing ECMO shortly after transplantation. We believe that this outcome is partially the result of our cannulation mode and suggest considering this approach in patients in whom the V-V ECMO does not provide a sufficient systemic oxygenation.

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